12-14-05

Confirm. No. 6199
512100-2025

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant(s)	:	BERTHOLD et al.
Serial No.	:	10/031,529
For	:	PHARMACEUTICAL COMPOSITION
Filed	:	10 May 2002
Examiner	:	Isis Ghali
Art Unit	:	1615

12/14/2005 HDEMESS1 00000039 10031529
01 FC:1254 1590.00 OP

745 Fifth Avenue
New York, NY 10151

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12/14/2005 HDEMESS1 00000039 10031529
02 FC:1402 500.00 OP

APPEAL BRIEF UNDER 37 C.F.R. §41.37
WITH REQUEST FOR EXTENSION OF TIME

Mail Stop Appeal Brief – Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Appeal Brief is filed in response to the Final Rejection of claims 13-23 in the Office Action dated 13 December 2004.

This Brief is submitted in triplicate.

This Brief is accompanied by a check for the requisite fee of $500.00 as set forth in 37 C.F.R. §41.20(b)(2). The Assistant Commissioner is authorized to charge any deficiency or credit any overpayment associated with this appeal to Deposit Account No. 50-0320.

PETITION FOR EXTENSION OF TIME

Pursuant to the provisions of 37 C.F.R. §1.136(a)(1), applicants hereby petition for an extension of time of four months in responding to the Notice of Appeal of 13 June 2005 Granting of Applicants' request would serve to extend Applicants' due date from 13 August 2005 to 13 December 2005.

Enclosed is a check in the amount of **$1590** to satisfy the fee for a four (4) month extension of time. The Commissioner is hereby authorized to charge any additional fee which may be required, or credit any overpayment to Account No. 50-0320.

(1) Real Party in Interest

The real party in interest in this appeal is the assignee, LTS Lohmann Therapie-Systeme AG (see Notice of Recordation of Assignment – Reel/Frame: 012963/0113).

(2) Related Appeals and Interferences

Appellants are not aware of any related appeals or interferences which directly affect or are directly affected or have bearing in the Board's decision in the pending appeal.

(3) Status of Claims

Claims 1-12 have been cancelled. Claims 13-23 are pending in this application and stand rejected under 35 U.S.C. § 103(a) for allegedly being obvious. The rejections of claims 13-23 are the subject of this Appeal Brief.

(4) Status of Amendments

No amendments to the claims were made after the final rejection of 13 December 2004 as there was no indication of allowable subject matter made by the Examiner.

NOTE: Upon review of the claims, the spelling of the compound "N-methyl-2-pyrrolidinone" is incorrect. In the interest of compact prosecution, the appellants authorize correction to ---N-methyl-2-pyrrolidone--- by Examiner's Amendment should the claims be held to be allowable.

(5) Summary of Claimed Subject Matter

Claim 13 is the only independent claim pending on appeal and reads as follows:

13. A transdermal therapeutic system for administering a calcium antagonist of the dihydropyridine type which comprises:

a) a backing layer, which defines the upper surface of the device,

b) a drug reservoir containing a solution comprising:

- a calcium antagonist of the dihydropyridine type,
- an alcohol selected from the group consisting of ethanol, propanol, isopropanol, and n-decyl alcohol,
- a pyrrolidone derivative, and
- a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and polyhydroxy alcohol,

c) a membrane to control the release of the active ingredient, and

d) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer

wherein the said backing layer and said membrane are connected together to form the drug reservoir.

Support for claim 13 can be found, e.g., in the specification on page 2, lines 9-17 and the claims originally submitted as part of WO 01/07017 (see claim 1).

Support for claim 14 can be found, e.g., in the specification on page 4, lines 9-12 (pages 8-10 of the specification) and the claims originally submitted as part of WO 01/07017 (see claim 2).

Support for claim 15 can be found, e.g., in the specification on page 4, lines 20-23 and the claims originally submitted as part of WO 01/07017 (see claim 3).

Support for claim 16 can be found, e.g., in the specification on page 2, lines 24-26 and the claims originally submitted as part of WO 01/07017 (see claim 4).

Support for claim 17 can be found, e.g., in the specification on page 1, lines 15-17 and the claims originally submitted as part of WO 01/07017 (see claim 5).

Support for claim 18 can be found, e.g., in the specification on page 2, lines 24-26 and the claims originally submitted as part of WO 01/07017 (see claim 6).

Support for claim 19 can be found, e.g., in the specification on page 2, lines 24-26 and the claims originally submitted as part of WO 01/07017 (see claim 6).

Support for claim 20 can be found, e.g., in the specification on page 1, lines 22-25 and the claims originally submitted as part of WO 01/07017 (see claim 10).

Support for claim 21 can be found, e.g., in the specification on page 3, lines 16-31 and the claims originally submitted as part of WO 01/07017 (see claim 11).

Support for claim 22 can be found, e.g., in the specification on page 4, lines 9-12 and the claims originally submitted as part of WO 01/07017 (see claim 12).

Support for claim 23 can be found, e.g., in the specification on page 2, lines 19-22 and the claims originally submitted as part of WO 01/07017 (see claim 14).

(6) Grounds of Rejection to Be Reviewed on Appeal

There are three grounds for rejection to be reviewed on appeal:

1. Whether claims 13-23 were properly rejected as being obvious under 35 U.S.C. §103 Ueda et al. (U.S. Patent 5,045,553) in view of Konno et al. (U.S. Patent 4,879,119);

2. Whether claims 13-23 were properly rejected as being obvious under 35 U.S.C. §103 over Chang et al. (U.S. Patent 4,983,395) in view of Konno et al. (U.S. Patent 4,879,119);
3. Whether claims 13-23 were properly rejected as being obvious under 35 U.S.C. §103(a) over Squillante et al. (EP 680 759) in view of Konno et al. (U.S. Patent 4,879,119).

(7) Argument

1. Claims 13-23 are not obvious under 35 U.S.C. 103(a) over Ueda et al. (U.S. Patent 5,045,553 - hereafter "Ueda") in view of Konno et al. (U.S. Patent 4,879,119 - hereafter "Konno")

a. Claims 13-23 all require that the drug reservoir contains a solution and the presence of a pyrrolidone derivative as part of the combination of skin penetration enhancer which is not taught by the prior art which is directed to semisolid compositions and different penetration enhancer combinations

Standard of Review

Two of the basic considerations which are required when making a determination of obviousness are that the claimed invention must be considered as a whole and the references must also be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. *see* MPEP 2141, section II and MPEP 2142.02.

Whether an invention would have been obvious under 35 U.S.C. §103 is a legal conclusion based on underlying findings of fact[1]. Establishing a *prima facie* case of obviousness also requires that all claim limitations must be taught or suggested by the prior art[2] and that the Examiner bears the initial burden of ***factually supporting*** any *prima facie* conclusion of obviousness[3].

Consideration of the applicants claimed invention as a whole

According to appellants' claims, the drug reservoir contains a **solution** and this solution has four required elements which must be present simultaneously: (1) a calcium antagonist of the dihydropyridine type; (2) an alcohol selected from the group consisting of ethanol, propanol, isopropanol, and n-decyl alcohol; (3) a **pyrrolidone** derivative; and (4) a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and polyhydroxy alcohol. (Elements (2), (3) and (4) constitute the skin penetration enhancer).

As acknowledged by the Examiner, Ueda does not teach specific pyrrolidone derivatives, sorbitan palmitate as specific enhancers or lacidipine and nifedipine species of dihydropyridines or the specific amounts of different ingredients as claimed. However, Ueda also does not teach that their pharmaceutical composition is in solution form.

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[1] *In re Kotzab*, 217 F.3d 1365, 1369, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000).

[2] *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), *see also* MPEP 2143.03.

[3] *see* MPEP 2142 (emphasis added) (also "If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness.").

Ueda recites that the state of the art with regard to dihydropyridine compounds is that one of ordinary skill in the art would have expected these compounds to be "...sparingly soluble in water and, as such, can be absorbed percutaneously only to a slight extent." Ueda's answer to this problem is to add ethanol and/or an unsaturated higher fatty acid (see col. 1, lines 7-17).

However, Ueda never provides a teaching which suggests that this answer resulted in a dihydropyridine ***solution***. The state of the art for dihydropyridine compounds is that these compounds were only sparingly soluble in water and the direction given by Ueda suggests the answer to the problem of solubility is to ignore trying to form a solution of a dihydropyridine compound and concentrate on forming of ***gels*** containing a dihydropyridine compound with ethanol and/or an unsaturated higher fatty acid (see col. 3, lines 17-20 and Examples 1-22).

Given the state of the art for dihydropyridine compounds, the direction and teaching from with Ueda and the lack of any factual support for the Examiner's assertion that Ueda's compositions are solutions, the compositions of Ueda also differ from the appellants' claimed invention in that they are not solutions.

Neither Ueda nor Konno alone or in combination suggest the specific combination of elements which constitutes the appellants' penetration enhancer. When considering the Konno reference as a whole, it is clear that the primary feature of their invention is the combination of a ***triglyceride of a fatty acid*** with a penetration enhancer, i.e. the state of the art with respect to Konno is that penetration enhancers were ineffective for use with dihydropyridine compounds and only the addition of a triglyceride of a fatty acid could salvage their use; even with this teaching, Konno still ***does not teach a solution but a dispersion***. In addition, Konno does not recognize pyrrolidones as penetration enhancers but as solvents (compare col. 2, lines 67-68 with col. 3, lines 11-20).

There is no teaching from within Konno which suggests the ***combination*** of (2) an alcohol selected from the group consisting of ethanol, propanol, isopropanol, and n-decyl alcohol; (3) a pyrrolidone derivative; and (4) a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and polyhydroxy alcohol nor is there any reason to "pick and choose" an isolated element from the teaching of Konno for insertion into Ueda. Moreover, selecting a permeation enhancer from within Konno for combination with Ueda would not have motivational support as Konno teaches the ineffectiveness of permeation enhancers without a

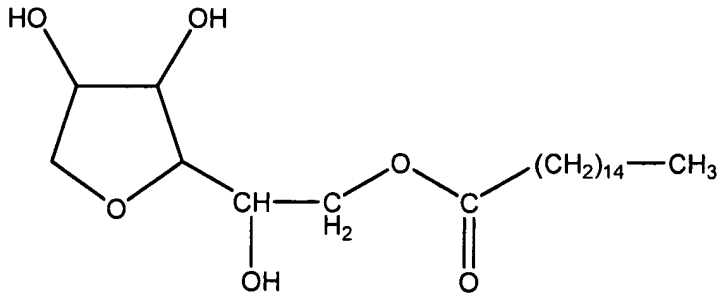
triglyceride of fatty acid; would not result in the selection of a pyrrolidone as it is described as a solvent and would lack any predictability that the gels of Ueda would have resulted in solutions.

Given the state of the art as described by Ueda and Konno regarding the solubility of the dihydropyridine compounds, even if it was permissible to "pick and choose" isolated elements from an invention making an as a whole determination of the Ueda and Konno references, one of ordinary skill in the art would seek to pick the element of a triglyceride of a fatty acid not another permeation enhancer.

Because the combination of Ueda and Konno do not teach each and every element of the appellants' claimed invention (especially with regard to being in solution form and the specific combination of elements comprising the penetration enhancers), the appellants claims are not rendered obvious by the combination of Ueda and Konno.

b. Claims 14, 15 and 22 are directed to specific alcohols, pyrrolidones and fatty acid esters which is even further removed from being obvious in view of Ueda and Konno

The arguments presented above regarding the rejection of claims 13-23 over Ueda and Konno still apply here. However, the appellants point out that for claims 14, 15 and 22, the alcohol is specifically ethanol, the pyrrolidone is N-methyl-2-pyrrolidone and the fatty acid ester is sorbitan ester (see figure below).



sorbitan palmitate

While it can be argued that the combination of Ueda and Konno specifically mention ethanol and N-methyl-2-pyrrolidone by name (even if it lacks a teaching for a specific combination of penetration enhancers), the same cannot be held true for sorbitan palmitate, i.e. it is not encompassed by the "unsaturated higher fatty acids" used in Ueda (see especially col. 2, lines 41-51) and is not encompassed by the triglyceride fatty acids or permeation enhancers described in Konno.

In addition, as noted above, Konno does not recognize N-methyl-2-pyrrolidone to be a penetration enhancer within the context of their invention.

Because the combination of Ueda and Konno do not teach each and every element of the appellants' claimed invention and would be too remote for one of ordinary skill in the art to contemplate when considering the appellants' claims at the time the invention was made without having benefit of the appellants' claims before them, the appellants claims are not rendered obvious by the combination of Ueda and Konno.

c. Claims 18 and 19 are directed to lacidipine and nifedipine as a specific dihydropyridine compounds which is even further removed from being obvious in view of Ueda and Konno

The arguments presented above regarding the rejection of claims 13-23 over Ueda and Konno still apply here. However, the appellants point out that claim 18 is directed to lacidipine and claim 19 is directed to nifedipine as the dihydropyridine compounds.

Lacidipine is never even mentioned in either Ueda or Konno whereas nifedipine is only mentioned in the Konno reference. The Examiner states that it would be obvious to substitute one drug for another absence any evidence to the contrary but offers no factual support for this position. In addition, the teachings of Ueda would suggest that making such a substitution is not obvious, i.e. whereas appellants composition was tested on both lacidipine and nifedipine, the Ueda reference was only relevant to nilvadipine; the specification and claims do not teach, suggest or hint that their formulations would be applicable to other compounds.

Because the combination of Ueda and Konno do not teach each and every element of the appellants' claimed invention and would be too remote for one of ordinary skill in the art to contemplate when considering the appellants' claims at the time the invention was made without having benefit of the appellants' claims before them, the appellants claims are not rendered obvious by the combination of Ueda and Konno.

2. Claims 13-23 are not obvious under 35 U.S.C. 103(a) over Chang et al. (U.S. Patent 4,983,395 - hereafter "Chang") in view of Konno et al. (U.S. Patent 4,879,119 - hereafter "Konno")

a. Claims 13-23 all require that the drug reservoir contains a solution and the presence of a pyrrolidone derivative as part of the combination of skin penetration enhancer which is not taught by the prior art which is directed to semisolid compositions and different penetration enhancer combinations

Chang and Konno is essentially a duplicate rejection of Ueda and Konno cited above. Chang differs from Ueda in that it is specifically directed to a transdermal drug delivery device and specifically mentions nifedipine, albeit in the context of a vast Markush group of potential compounds (see col. 4, line 57 through col. 5, line 32). The Examiner acknowledges that Chang does not teach pyrrolidone derivatives, sorbitan palmitate as specific enhancers or lacidipine as a species of dihydropyridine. Chang also does not teach that their pharmaceutical composition is in solution form but in gel form which is consistent with the state of the art represented by Ueda. Likewise, the combination of Chang with Konno does not serve to teach each and every limitation of the applicants' claims for substantially the same reasons described above for Ueda and Konno.

b. Claims 14, 15 and 22 are directed to specific alcohols, pyrrolidones and fatty acid esters which is even further removed from being obvious in view of Chang and Konno

The arguments made above with respect to Ueda and Konno also address the rejection made over Chang and Konno.

c. Claims 18 and 19 are directed to lacidipine and nifedipine as a specific dihydropyridine compounds which is even further removed from being obvious in view of Chang and Konno

The arguments made above with respect to Ueda and Konno also address the rejection made over Chang and Konno.

3. Claims 13-23 are not obvious under 35 U.S.C. 103(a) over Squillante et al. (EP 680 759 - hereafter "Squillante") in view of Konno et al. (U.S. Patent 4,879,119 - hereafter "Konno")

a. Claims 13-23 all require that the drug reservoir contains a solution and the presence of a pyrrolidone derivative as part of the combination of skin penetration enhancer which is not taught by the prior art which is directed to semisolid compositions and different penetration enhancer combinations

Squillante and Konno is essentially a duplicate rejection of Ueda and Konno cited above. Squillante specifically mentions nifedipine but is very similar to Ueda in that the preferred fatty acid is oleic acid, an alcohol is used, preferably propylene glycol (in this regard Squillante is more removed than Ueda as propylene glycol is not within the scope of appellants' claims 13-23). The Examiner acknowledges that Squillante does not teach pyrrolidone derivatives, sorbitan palmitate as specific enhancers or lacidipine as a species of dihydropyridine. Squillante also does not teach that their pharmaceutical composition is in solution form but in gel form which is

consistent with the state of the art represented by Ueda and Chang. Likewise, the combination of Chang with Konno does not serve to teach each and every limitation of the applicants' claims for substantially the same reasons described above for Ueda and Konno.

b. Claims 14, 15 and 22 are directed to specific alcohols, pyrrolidones and fatty acid esters which is even further removed from being obvious in view of Squillante and Konno

The arguments made above with respect to Ueda and Konno also address the rejection made over Squillante and Konno. Squillante is even futher removed with respect to the alcohol as propylene glycol is preferred which is not in any of the appellants' claims.

c. Claims 18 and 19 are directed to lacidipine and nifedipine as a specific dihydropyridine compounds which is even further removed from being obvious in view of Squillante and Konno

The arguments made above with respect to Ueda and Konno also address the rejection made over Squillante and Konno.

Conclusion

Although the duplicative nature of the rejections would normally be objected to, in the present case, they merely reinforce the appellants' position that one of ordinary skill in the art would not have contemplated the appellants combination of penetration enhancers for combination with a dihydropyridine drugs and it is well recognized in the art that such combinations are not obvious over different combinations in the art.

For the reasons discussed in this Brief and the arguments of record (incorporated herein by reference), claims 13-23 are patentable over either: (1) Chang et al. (U.S. Patent 4,983,395) in view of Konno et al. (U.S. Patent 4,879,119); (2) Ueda et al. (U.S. Patent 5,045,553) in view of Konno et al. (U.S. Patent 4,879,119); and (3) Squillante et al. (EP 680 759) in view of Konno et al. (U.S. Patent 4,879,119). It is therefore, respectfully submitted that the Examiner's rejection of claims 13-23 should be reversed by this Honorable Board, and prompt issuance of a Notice of Allowance is earnestly solicited.

Respectfully submitted,

FROMMER LAWRENCE & HAUG LLP
Attorneys for Appellants

By: Howard C. Lee

Marilyn M. Brogan
Reg. No. 31,233

Howard C. Lee
Reg. No. 48,104
(212) 588-0800

(8) Claims Appendix

Claims 1-12 (Canceled)

Claim 13 (previously presented)

13. A transdermal therapeutic system for administering a calcium antagonist of the dihydropyridine type which comprises:

    e) a backing layer, which defines the upper surface of the device,

    f) a drug reservoir containing a solution comprising:

    - a calcium antagonist of the dihydropyridine type,
    - an alcohol selected from the group consisting of ethanol, propanol, isopropanol, and n-decyl alcohol,
    - a pyrrolidone derivative, and
    - a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and polyhydroxy alcohol,

    g) a membrane to control the release of the active ingredient, and

    h) a pressure sensitive adhesive layer for attaching the system to the skin and, if necessary, a release liner on the outer face of the adhesive layer

    wherein the said backing layer and said membrane are connected together to form the drug reservoir.

Claim 14 (previously presented)

14. A transdermal therapeutic system as claimed in claim 13 wherein the solution in the drug reservoir comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate.

Claim 15 (previously presented)

15. A transdermal therapeutic system as claimed in claim 14 wherein the solution comprises a calcium antagonist of the dihydropyridine type 3 – 5%, ethanol 30 – 40%, sorbitan palmitate 3 – 5% and N-methyl-2-pyrrolidinone 50 – 60% by weight of the total solution.

Claim 16 (previously presented)

16. A transdermal therapeutic system as claimed in claim 13 which is the form of skin patch.

Claim 17 (previously presented)

17. A transdermal therapeutic system as claimed in claim 13 in which the calcium antagonist of the dihydropyridine type is selected from the group consisting of amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, and nitrendipine.

Claim 18 (previously presented)

18. A transdermal therapeutic system as claimed in claim 17 in which the calcium antagonist of the dihydropyridine type is lacidipine.

Claim 19 (previously presented)

19. A transdermal therapeutic system as claimed in claim 17 in which the calcium antagonist of the dihydropyridine type is nifedipine.

Claim 20 (previously presented)

20. A method for administering a calcium antagonist of the dihydropyridine type through a pre-determined area of intact skin and at an administration rate which will reach and maintain an effective therapeutic dose of a calcium antagonist of the dihydropyridine type for the control of hypertension and cardiovascular diseases selected from the group consisting of atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure which comprises applying to the skin a transdermal therapeutic system as claimed in claim 13.

Claim 21 (previously presented)

21. A solution which is suitable for use in a drug reservoir for a transdermal therapeutic system as claimed in claim 13 which comprises:

- a calcium antagonist of the dihydropyridine type,

- an alcohol selected from the group consisting of ethanol, propanol, isopropanol and n-decyl alcohol,
- a pyrrolidone derivative, and
- a saturated or unsaturated fatty acid ester of a carboxylic acid containing 8 – 16 carbon atoms and a polyhydroxy alcohol.

Claim 22 (previously presented)

22. A solution as claimed in claim 21 which comprises a calcium antagonist of the dihydropyridine type, ethanol, N-methyl-2-pyrrolidinone and sorbitan palmitate.

Claim 23 (previously presented)

23. A method of treating hypertension which comprises administering an effective amount of calcium antagonist of the dihydropyridine type in a transdermal therapeutic system as claimed in claim 13.

(9) Evidence Appendix

(10) Related Proceedings Appendix

None